Genotype-phenotype relationships and their clinical implications in inflammatory bowel disease and type 2 diabetes

Abedian, Shifteh

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Chapter 8

General Discussion

Summary of main findings

This thesis evaluated the epidemiology and effect of genetic variants on disease sub-phenotypes, disease course and disease complications of two complex diseases: inflammatory bowel disease (IBD) and type 2 diabetes (T2D). In this final chapter, I will reflect on the most important findings.

Following an introduction to the concept of clinical application of genetic findings in complex disease in **Chapter 1**, I evaluated the changes of the admission rate for complex gastrointestinal and liver disease that required admission in a typical tertiary referral hospital over a period of 10 years in **Chapter 2**. In this study, I aimed to evaluate the etiology and outcome of gastrointestinal and liver disease to help health policy makers to improve health planning and to provide an opportunity for further research on the environmental and genetic risk factors of gastrointestinal diseases in Iran. I performed a retrospective study in hospital registry data of 5,880 patients admitted to one referral hospital from 2000 to 2009. I found UC admission rate have remained stable over the study period. The rate of admission due to CD increased from 1.93% (of total GI disease admissions) in 2000 to 2.72% in 2009. Despite reports of low prevalence and incidence rates of IBD from Asia[1], some other reports from Iran are in line with my own findings and have shown an increasing rate of CD[2, 3]. Of note, my study had limitations, which included not being population-based, and is conducted in only one large tertiary hospital in Iran.

In Chapter 3, I further focused on the epidemiology of UC in Iran. I performed a qualitative systematic review of the epidemiology and risk factors for UC including published studies from 1987 to 2012. I aimed to evaluate and investigate the incidence, prevalence, and demographic characteristics of UC in Iranian patients. The prevalence and incidence of UC showed an increasing pattern similar to other countries in the region. Although the incidence of IBD is rising in developing countries, comparable data on the clinical phenotype of disease in European and non-European populations had so far been limited.

In **Chapter 4**, as part of a large international consortium, we described the first Trans ethnic genome wide association study of 4,686 patients with IBD from East Asia, India and Iran as compared to 35,128 Europeans. We showed some demographic differences and less inflammatory CD in non-European populations. In UC, there was a low rate of extensive colitis reported and a lower rate of colectomy in non-Europeans. Furthermore, we identified 38 novel single nucleotide polymorphisms (SNPs), increasing the number of known IBD risk loci to 200. The

majority of these loci were shared across diverse ancestry groups. Together, these loci explain 13.1% and 8.2% of the variance in disease liability for CD and UC, respectively. Such trans-ancestry association studies have successfully identified susceptibility loci for other complex diseases, including T2D and rheumatoid arthritis[4, 5].

Recently, the genetic risk score (GRS) approach has increasingly been used to aggregate the contribution of multiple SNPs by combining genetic information and to test for improved performance in predicting incidence of disease. Understanding the role of GRS in predicting IBD and its complications may improve the identification of high-risk individuals and thereby aid in prohibiting occurrence of complications and preventing recurrence of the disease.

In **Chapter 5**, I undertook a cross-population study to further understand whether GRSs of IBD, and CD and UC separately, could explain the percentage of disease occurrence, and if they contribute to prediction of the occurrence of disease in general populations from East and Central Asia. I found a multilocus GRS for IBD to be significantly but only mildly associated with IBD risk. I found that the association of GRS is unlikely to provide a strong predictor for IBD, CD and UC in East and Central Asians.

In **part 2** of my thesis, I focused on prediction of disease course or complications of T2D. T2D and its related comorbid diseases are caused by the interplay of both genetic and environmental factors over the lifespan. To date GWASs have identified 243 genetic loci associated with T2D[6]. Yet, the role of individual genetic variants as determinants of major micro- and macrovascular complications remains to be understood.

In **Chapter 6**, I aimed to examine the associations between genetic variants and the incidence of major co-morbid diseases related to T2D including cardiovascular disease (CVD), cancer, chronic kidney disease, chronic eye disease and neurological diseases. I showed that half of the patients with T2D developed at least one comorbid disease. In this study, CVD was the most common and earliest comorbid condition associated with T2D, followed by chronic eye disease and cancer. In the discovery study, I identified a total of 39 variants associated with comorbid diseases. In the replication study, however, only two SNPs originally associated to chronic eye disease were nominally significant. Thus, these results did not provide strong evidence that genetic susceptibility is among major factors that underlie the incidence of comorbid conditions in T2D.

Pharmacologically T2D is treated with nine major classes of approved drugs, including insulin and its analogues, and oral anti-diabetic drugs (OAD). OADs are

among the most widely prescribed, including Metformin (MET), Sulfonylurea (SU) and Thiazolidine (TZD).

In **Chapter 7**, I aimed to determine changes in HbA1c levels using individual patient data stretching over a total of 25 years, since HbA1c reflects glycemic control and is one of the most important predictors of development of complications of T2D. Using a multi-step model building process provided a final model with main and interaction effects on HbA1c levels. I concluded that the initial monotherapy with either MET or TZD alone or even a combination of INS with MET, or INS with SU fails to achieve a low HbA1c level in the long term. INS remains an important part of treatment for T2D, either alone, or in combination with TZD. To prohibit development of INS resistance, a combination of TZD with MET or SU appeared to be the most effective alternative in reducing HbA1c.

Epidemiology of IBD in developing countries

IBD has been recognized as a chronic, progressive inflammatory intestinal disorder. It is a heterogeneous disease without identifiable causes at the clinical level, which confers a significant burden for the patient. The incidence of CD and UC varies across the world; both CD and UC have emerged as global diseases. The prevalence and incidence of IBD vary locally and ethnically[7]. IBD causes significant morbidity and increased markedly in prevalence among all populations in recent years[8]. IBD was traditionally regarded as being prevalent in mainly Western countries[9]. However, recent decades have been characterized by increasing incidence rates of IBD in newly industrialized countries such as in Asia[10, 11, 12]. Though limited data were available on the hospitalization or re-hospitalization rates of CD and UC from population-based studies in Iran, I found relatively high rates of CD-related hospitalizations and re-hospitalizations in Iran aligned with its rising incidence globally, as I found in other studies[2].

A gradual increase in the incidence and prevalence of CD in developing countries has coincided with an improvement in public health, and a more Western life style in nations such as India[13], Japan[14], and South Korea[15]. The Iranian people have rapidly improved their health status over the past century, which coincides with reports of an increasing burden of this disease[3]. This increasing trend in IBD prevalence necessitates specific health care planning in Asia. We, therefore, need to gain a clear understanding of the individual clinical and therapeutic characteristics of Asian patients with IBD, compared to Caucasians patients. In these regions, comprehensive nationwide registries of patient reported outcomes in combination with clinical data therefore need to be set up for a better definition of disease characteristics, course, outcomes and management of IBD.

Accordingly, I summarized current knowledge of the phenotypic appearances and management practices of patients with IBD in **Chapter 2**, **Chapter 3** and **Chapter 4**, with a special focus on a comparison of Eastern and Western perspectives in **Chapter 4** and **Chapter 5**. The findings of our study are in line with other studies. In Asia, the incidence of UC is higher than that of CD[16]. In addition, UC patients in Asia have better prognosis than those in western countries[16]. There is no difference in the prevalence of CD according to sex in the West[9]. However, in Asia CD is more common in men. In **Chapter 4**, we showed the role of genetic factors as an important cause of both CD and UC in Asian populations as well, with stronger effects in CD. Yet the strength of the contribution of individual genetic variants to susceptibility of IBD in Asians was different from those observed in Europeans. These genetic and clinical differences suggest that using the same Western guidelines of management strategies of IBD for these different populations may not be appropriate. Moreover, investigation of the Asian-specific clinical characteristics of IBD suggests the possibility of identifying relevant factors in the pathogenesis of IBD in this area[9].

Genotype–Phenotype Associations

In recent years, methodological advances in genetic analysis have impressively expanded our knowledge of IBD genetics. Clearly, the next logical step would be identifying genotype–phenotype relations, in the hope that these could be translated into clinical practice. Genotype–phenotype association studies suggest that some of the genetic alleles contributing to the onset of IBD also have an impact on disease severity and are linked to an increased risk of disease complications. Despite important developments in the past two decades, the complexity of IBD creates vast challenges, and traditional scientific methods have been unable to satisfactorily address important question regarding clinical management needs[17]. Following the introduction of GWAS, the number of significant genetic risk loci in IBD has expanded progressively. Association studies have previously identified more than 240 IBD susceptibility loci in European ancestry populations[18]. Some genetic variants proved to be associated with diverse disease phenotypes[19]. At least 35 loci have been identified in Asians[7]. Most loci are shared between CD and UC and overlap with loci associated with other immune-mediated diseases[20].
Although the genetic risk loci for IBD overlap between Asians and Westerners, genetic heterogeneity has been discovered in many risk loci. Thus, although common pathways exist between Westerners and Asians in the progress of IBD, their implications may differ for disease specific pathways, across continents[20]. The phenotypic characteristics reported in familial cases of IBD suggested shared environmental and genetic factors shape disease phenotype of CD and UC[21]. In CD,

the most predictable finding from genotype–phenotype studies is the separate genetic profile of ileal CD in comparison to colonic CD, suggesting that the two subtypes of CD have a different disease presentation[22, 21]. It is unclear whether Asian-specific clinical characteristics of IBD are totally due to the differences in environmental factors, emphasizing the need for genetic studies of IBD in Asian populations[7]. Therefore, in **Chapter 5**, I focused on data from Asian countries to study genetic prediction of IBD so these results might eventually be applied in clinical medicine.

Implications of genetic findings for phenotype prediction

One the most important applications of big data methodologies in health care is to develop predictive models that identify high-risk patients, by including previously unconsidered variables and complex information such as genetic data[23]. Moreover, genetic studies have identified SNPs responsible for the increase in risk. Since many genetic variants have small effect sizes and each variant accounts for only a small part of the disease heritability, it is now common to use GRS to estimate population-specific effects.

GRS has been shown to explain disease heritability and it helps to dissect genetic overlap between sub-phenotypes[24,25]. My study found that GRS could explain between 1.19–4.40% of IBD disease variance in Asian populations in **Chapter 5**, and 10% in European populations in **Chapter 4** given that many more IBD-associated SNPs have been identified in European populations. The percentages of disease variance explained are comparable between CD and UC in our Asian populations, suggesting a similar contribution of the risk alleles to both diseases[26]. These percentages are similar to those reported for other common diseases, such as T2D[27, 28], coronary heart disease[29,30], and breast cancer[31].

The small proportion of variance explained reveals the presence of significant missing heritability[32], which may be due to genetic epistasis, gene-environment interaction, or the presence of unmapped genetic loci, structural, and/or rare variants, especially those with dominant effect and inadequate accounting for shared environment[33]. Importantly, the rapid rise of IBD incidence in Asia points to the importance of a changing environment, suggesting the possibility of gene-environment interaction in its pathogenesis[34, 35, 36].

Likewise, despite much-anticipated interest, predicting the outcomes may not be achievable based on the current data. I found that IBD GRS showed little additive value in predicting IBD, or CD and UC separately, in the general Asian population. The low predictive proportions may also be attributable to our relatively small sample size, that leads to fluctuations in estimates, the small size of the non-Caucasian discovery GWAS and the limited transferability of GRS across

different ethnicities[37]. This notion agrees with studies on other conditions, including breast cancer[38], diabetes mellitus[39, 40], coronary heart disease[41, 34], and multiple sclerosis[42], that found limited improvement in risk prediction with using GRS.

As noted by us and others[43], the predictive utility of GRS for common diseases is likely to be very limited, especially considering the myriad factors of the exposome that also influences individual susceptibility[44]. The power of the GRS in predicting IBD risk and hence its clinical usefulness was thus limited. We showed the association of GRS is unlikely to provide a strong predictive probability of IBD, and CD and UC separately, in Central and East Asians.

The future of genetics in disease management

In both IBD and T2D, the current trend is to move toward a personalized and more aggressive treatment, with the final aim of changing disease course and returning to a normal life[45]. It is currently anticipated that a combination of information on genetic liability, integrated with clinical characteristics and with environmental exposures such as lifestyle and dietary habits is needed to perform optimal disease management in IBD and T2D.

Obtaining a patient's genetic risk profile enables early diagnosis before the full clinical picture arises allowing implementation of early treatment and prediction of possible responses to different drugs. Thus treating physicians could tailor prescriptions to patient characteristics to prevent adverse events, attain optimal dosing, and optimize efficacy. Despite recent advances in the discovery of genetic factors underlying disease onset and the severity of disease course in complex diseases, clinical applications of research findings is still at an early stage.

In my study of the pharmacology of glycemic control of T2D patients in **Chapter 7**, I found, in agreement with several previous studies, that initial monotherapy with either MET[46] or TZD[47] alone or even a combination of INS with MET[48], or INS with SU[49] fails to achieve a well-controlled glycaemia in the long term. INS[50] remains an important part of treatment for T2D, either alone, or in combination with TZD[51], and is certainly a needed option for many patients. Nevertheless, I showed that not every patient may benefit from the same type of glucose management. Certain patients present a different disease course and need different, perhaps more personalized care.

Individual characteristics may affect clinical outcome and therapeutic response. In this context, knowledge on genetics could help determine whether: i) patients with certain disease subtypes are more likely than others to be responsive to a particular medication, and; ii) individuals can be classified into subpopulations that are susceptible to a particular disease or responsive to a specific treatment.

This approach (i.e., pharmacogenetics) examines individual genetic variations affecting efficacy and safety of medication. To date, major pharmacogenetic studies have focused on response to SU[52, 53], MET[54, 55], and TZD[56,57]. Accordingly, combining genetic variants affecting the OAD-efficacy may improve the clinical application of these drugs. These results, if confirmed in future studies, can be useful in individualized pharmacologic management of T2D.

Yet, pharmacogenetics is not routinely used in clinical practice of T2D. Such research is important to allow translation of the benefits of genetic research into improved risk prediction, targeted therapies and eventually disease preventive strategies for the entire population. Importantly, the results should guide the improvement of guidelines for the design, conduct, and reporting the pharmacogenetics studies of T2D. Currently, clinical implications of the present findings are still limited despite a growing number of associated risk factors.

Concluding words: Do our findings help realize a more individualized approach in the clinic?

In recent years, methodological advances in genetic analysis have greatly expanded our understanding of the genetic background of IBD and T2D. Significant inter-individual heterogeneity can be observed in disease outcome. Although genetic studies are not completely appreciated in clinical practice, they may be useful for diagnosing and categorizing IBD, predicting therapeutic responses and assessing prognosis of T2D by risk modeling, thus facilitating precision medicine for individual patients.

Translation of results from genetic findings to medical practice is highly recommended. Not only should we investigate how genetic factors influence the disease outcome of interest (like IBD, or T2D), but we should also study genetic risk factors associated with complications, comorbidities, and drug metabolism. It is now more important than ever to start incorporating genetic advances into routine clinical practice, to enable more personalized approaches to manage complex diseases such as IBD and T2D.

This means, however, that any proposed strategies that use common genetic variants for informing clinical decisions would need to be rigorously tested beforehand. Greater efforts will be required to use the available genetic information in an appropriate clinical context to optimize disease prevention and management.

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